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The inter-relationships of tardive dyskinesia, parkinsonism, akathisia and tardive dystonia: the Curaçao Extrapyramidal Syndromes Study II

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Abstract

A study of the four extrapyramidal syndromes (EPS), tardive dyskinesia, parkinsonism, akathisia and tardive dystonia, was performed in the Netherlands Antilles, a well-defined catchment area with only one psychiatric hospital. The population under study ($N=194$; mean age 53.1) was mainly Afro-Caribbean, and most patients were chronic. The severity of each EPS was measured with valid and reliable rating scales. The purpose was to study both the strength of the inter-relationships of EPS and the prevalence of combinations of EPS. The inter-relationships between the EPS were analyzed by means of logistic regression. The adjusted odds ratios between the various EPS revealed strong connections between the hyperkinetic syndromes (tardive dyskinesia, tardive dystonia and akathisia). Parkinsonism was found to be inversely related to tardive dyskinesia and to tardive dystonia. Almost 30% of the patients suffered from two or more EPS. The highest prevalence rates of combinations were: tardive dyskinesia combined with parkinsonism 12.9%, tardive dyskinesia combined with tardive dystonia 9.8%, and tardive dyskinesia combined with akathisia 5.2%. Our findings show a strong positive correlation between hyperkinetic forms of EPS. Furthermore, chronic psychiatric inpatients regularly suffer from combinations of EPS. Different treatment strategies are suggested for various combinations of EPS. © 1997 Elsevier Science B.V.

Keywords: Extrapyramidal syndromes; Tardive dyskinesia; Tardive dystonia; Parkinsonism; Akathisia; Prevalence

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1. Introduction

Extrapyramidal syndromes (EPS) that are related to the long-term use of neuroleptics can be classified by the time of onset (acute vs. tardive) and by phenomenology. In a study of mainly chronic psychiatric patients a phenomenological classification is preferable; EPS can be divided into four categories: tardive dyskinesia, parkinsonism, (tardive) akathisia and tardive dystonia. If a patient suffers from one of these EPS, the treatment, if available, is often straightforward. However, having several EPS simultaneously may give rise to clinical dilemmas (Lang and Weiner, 1992). Many prevalence studies have investigated one EPS only (Lang and Weiner, 1992; Task Force on Tardive Dyskinesia, 1992) and some studies have investigated two (Gardos and Cole, 1992; McCreadie et al., 1982; Toenniessen et al., 1985; Chiu et al., 1992; Yassa et al., 1986) or three EPS (Kucharski et al., 1987; Brown and White, 1992; Mukherjee et al., 1982; Ayd, 1961; McCreadie et al., 1992). In most cases the EPS concerned was tardive dyskinesia and or parkinsonism. Only two studies have measured all four EPS simultaneously (Sethi et al., 1990; Inada et al., 1991). However, neither study used valid scales to assess all four EPS and neither was located in a well-defined catchment area. Only two studies have measured the prevalence of EPS in a well-defined catchment area (McCreadie et al., 1992; O'Hara et al., 1993). O'Hara et al. (1993) measured two EPS and McCreadie et al. (1992) three EPS. None of the studies (McCreadie et al., 1992; Sethi et al., 1990; Inada et al., 1991; O'Hara et al., 1993) used multivariate techniques to analyze the inter-relationships. If a study design is to overcome the limitations mentioned above, it should satisfy three criteria:

(1) All four EPS should be measured simultaneously using valid and reliable rating scales.
(2) The study should be conducted in a geographically circumscribed area.
(3) Multivariate statistical analysis should be used, because multiple intercorrelated variables are involved.

Some of the earlier studies fulfill one criterion, but no study fulfills two criteria, let alone all three. We designed a study that fulfilled all three criteria in order to estimate the strength of the inter-relationships between the EPS and how often combinations of EPS occur. Our study was performed in the Netherlands Antilles, a well-defined catchment area with only one psychiatric hospital and a health-care system based on Western principles. Therefore, the area is uniquely suitable for epidemiological research. All four EPS were measured simultaneously with the use of valid and reliable rating scales. The purpose of the study was to assess the strength of the inter-relationships between EPS and to estimate the prevalence of each combination of EPS.

2. Methods

2.1. Patients and methods

The methods have been described in detail previously (van Harten et al., 1996a). In short, the study was performed in the Dr. D.R. Capriles psychiatric hospital located on Curaçao. The population of Curaçao is mainly of Afro-Caribbean origin. Most patients (75%) in the clinic were born on Curaçao. Twelve percent of the patients came from Aruba, an island that formerly belonged to the Netherlands Antilles but now has a special status.

On 1 June 1992 there were 214 psychiatric inpatients in the Dr. D.R. Capriles Clinic. Almost all patients (95%) were of Afro-Caribbean origin. The inclusion criteria for this study were: (i) no organic disorders that could cause movement disorders; (ii) a history of neuroleptic use for at least 3 months; and (iii) informed consent. There were 194 patients who fulfilled the inclusion criteria (van Harten et al., 1996a).

The research criteria and the case definitions of each EPS have been described in detail previously (van Harten et al., 1996a). Tardive dyskinesia was assessed with the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976; Schooler and Kane, 1982), parkinsonism with the motor examination part of the Unified Parkinson Disease Rating Scale (UPDRS) (Fahn, Elton and mem-

bers of the UPDRS Development Committee, 1987), akathisia with the Barnes Akathisia Rating Scale (Barnes, 1989; Halstead et al., 1994) and tardive dystonia with the Fahn–Marsden scale (Burke et al., 1985; Burke, 1992).

Four raters had been trained for a week in the use of a movement disorder examination protocol at the Dystonia Clinical Research Center at Columbia University, New York (Director: Dr. S. Fahn). Each patient was examined simultaneously by two raters. The way in which the inter-rater reliability was measured has been described previously (van Harten et al., 1996a). The inter-rater statistics were assessed with Cohen's kappa. Our kappas were: tardive dystonia 0.78, tardive dyskinesia 0.50, UPDRS 0.53 (tremor 0.70, rigidity 1.0) and akathisia 0.65.

The medical files were reviewed by two medical doctors who had no knowledge of the existence of movement disorders in the patients. The following data were collected about each patient: age, sex, age on first admission to the psychiatric hospital, number of admissions, total duration of stays in the clinic, and duration of the last stay. The DSM-III-R diagnosis at the time of the study (American Psychiatric Association, 1987) was assessed on the basis of the chart notes, and confirmed at a consensus meeting attended by the first author (P.N.vH.) and the treating psychiatrist. Furthermore, diabetes mellitus and leukotomy were measured as separate variables because they occurred fairly frequently and are known to influence the prevalence of tardive dyskinesia (Ganzini et al., 1992). Finally, the use of medication was assessed, neuroleptics being converted into chlorpromazine equivalents (CPZEQ), and anticholinergics, benzodiazepines, antidepressants and other medication being converted into yes/no variables (Davis, 1976; Moleman and Pepplinkhuizen, 1987).

2.2. Data analysis

The relationships between the various EPS were analyzed by multiple logistic regression analysis (Hosmer and Lemeshow, 1989). This was done in the following way: a specific EPS (e.g., tardive dyskinesia defined by case definition) was entered into the analysis as the dependent variable. Another EPS (e.g., parkinsonism) was entered as the independent variable, together with the following potential confounders: age, sex, age on first admission, number of admissions, total duration of stay(s) (in years) and duration of the last stay (in years), psychiatric diagnosis (for each category see Table 1), diabetes mellitus, leukotomy, neuroleptic dose in chlorpromazine equivalents, anticholinergics, benzodiazepines, lithium, antidepressants and other medication. The resulting regression coefficient for the independent variable (e.g., parkinsonism) describes the relationship between tardive dyskinesia and parkinsonism corrected for the confounding effects of the other variables in the equation. Trend tests were carried out to see whether a gradual change in one EPS alters the probability of having another. Trend tests were computed by treating each EPS (when

Table 1
Characteristics of the study population ($N=194$)

Characteristic	%	Mean	SD
Males	72.7		
Psychiatric diagnosis DSMIIIR[a]:			
Schizophrenia	77.3		
Affective disorder	5.2		
Dementia	8.2		
Mental retardation	4.6		
Cocaine abuse[b]	13.9		
Other	24.7		
Leukotomy in the past	11.9		
Diabetes mellitus	9.3		
Current medication			
Neuroleptics	86.1		
Depot medication	55.7		
Anticholinergics	34.0		
Benzodiazepines	19.1		
Antidepressants	4.6		
Lithium	10.3		
Other	22.2		
Age (years)		53.1	16.7
Age on first admission (years)		26.6	11.1
Total duration of stays in hospital (years)		20.1	16.5
Duration of last stay in hospital (years)		15.6	16.2
Number of times admitted		5.1	4.3
Neuroleptic dose (CPZEQ mg/day)[c]		698	695

[a] A patient can have multiple diagnoses.
[b] On Curaçao, addiction to drugs refers almost exclusively to cocaine (mostly used as base) and cannabis.
[c] Of the 86% of the patients currently using neuroleptics.
CPZEQ = chlorpromazine equivalents.

it was put into the analysis as an independent variable) as an ordinal variable, by which the total score was recoded in three categories (0, 1, 2, with 0 as the reference group. 0 = zero point on the scale, 1 = 1 to median, 2 = median to highest score. The median was calculated using all patients with a score higher than zero).

This paper focuses on the inter-relationships of EPS controlled for all other factors measured. Therefore, the contribution of these other factors to the prevalence of each EPS will not be discussed.

3. Results

Table 1 shows the characteristics of our sample. Of the 108 patients using depot neuroleptics, 42% used fluphenazine and 23% haloperidol. Less than 15% of patients were on the depot neuroleptic zuclopentixol, flupentixol or penfluridol. Oral neuroleptics alone were used by 59 patients. Of these 59 patients 46% used haloperidol. Risperidone, the only atypical neuroleptic, was used by nine patients.

Table 2 shows the odds ratios (OR), adjusted for the variables mentioned, of tardive dyskinesia with other EPS and consecutively of parkinsonism, akathisia and tardive dystonia with other EPS.

Life-time medication data concerning the neuroleptics and the anticholinergics were available in 161 patients. The mean life-time dose of neuroleptics was 3.3 kg CPZEQ (SD = 3.2) and the mean life-time dose of anticholinergics was 22.64 g benztropine equivalents (SD = 22.60) (for conversion table to benztropine equivalents see Moleman and Pepplinkhuizen, 1987). When life-time medication data are added as potential confounders and the analysis of Table 2 is repeated (then the analysis involves only the 161 patients for whom life-time medication data were available) the results do not change significantly.

Of the 77 patients with tardive dyskinesia, 39% had that disorder only, 17% had tardive dyskinesia with parkinsonism only. Other combinations with tardive dyskinesia were relatively rare (fewer than seven patients).

Of the 70 patients with parkinsonism, 53% had parkinsonism only, 19% had parkinsonism with tardive dyskinesia only. Any other combination with parkinsonism was found in fewer than ten patients.

Of the 18 patients with akathisia, 33% had this disorder only, 28% had akathisia with tardive dyskinesia only. Any other combination with akathisia was seen in fewer than four patients.

Of the 26 patients with tardive dystonia, 19% had tardive dystonia only, 27% had tardive dystonia with tardive dyskinesia only. Any other combination with tardive dystonia was seen in fewer than six patients.

Of the total population, 26% had no EPS, 45% had one, 20% two, 8% three and one patient (0.5%) had all four syndromes.

Table 3 shows the prevalence of all possible combinations of EPS.

4. Discussion

This study examined both the inter-relationships of various EPS and the prevalence of combinations of EPS in the entire psychiatric inpatient population of a well-defined catchment area. We have found statistically and clinically significant associations between the hyperkinetic syndromes (tardive dyskinesia, tardive dystonia and akathisia). Clinically significant is the finding that having tardive dyskinesia increases the probability of akathisia six-fold. This conclusion may help in the differential diagnosis of akathisia. Akathisia is often overlooked or misdiagnosed (and then treated incorrectly) as psychotic restlessness. Our finding indicates that any clinician diagnosing tardive dyskinesia in a patient should also search for akathisia. However, according to the following analysis this conclusion may be valid only in patients receiving moderate to high doses of neuroleptics. The unadjusted odds ratio between tardive dyskinesia and akathisia was not significant. Therefore, we assessed which factor in the logistic regression analysis increased the adjusted OR between tardive dyskinesia and akathisia. The neuroleptic dose appeared to be a strong factor. In fact, when the neuroleptic dose was converted into a dichotomous variable, a strong interaction effect appeared (neuroleptic dose split into above

Table 2
Adjusted odds ratios (OR) with 95% confidence intervals (95% CI)[a]

Independent variable	Dependent variables			
	Tardive dyskinesia OR (95% CI)	Parkinsonism OR (95% CI)	Akathisia OR (95% CI)	Tardive dystonia OR (95% CI)
Tardive dyskinesia[b]	—	0.6 (0.3–1.3)	6.2 (1.6–24.1)	8.7 (2.3–32.1)
AIMS (1)[c]	—	0.5 (0.2–1.2)	2.2 (0.5–10.1)	1.7 (0.4–7.3)
AIMS (2)[c]	—	0.4 (0.2–1.0)	22.9 (3.3–156.6)	11.0 (2.5–49.2)
Parkinsonism[b]	0.7 (0.3–1.4)	—	0.4 (0.1–1.6)	0.9 (0.3–2.7)
UPDRS (1)[d]	0.4 (0.2–1.0)	—	0.4 (0.1–1.8)	0.1 (0.0–0.5)
UPDRS (2)[d]	0.4 (0.1–0.9)	—	0.5 (0.1–2.1)	0.3 (0.1–1.2)
Akathisia[b]	6.6 (1.8–24.0)	0.4 (0.1–1.5)	—	1.7 (0.3–10.5)
Tardive dystonia[b]	7.5 (2.0–28.5)	1.1 (0.4–3.1)	1.3 (0.2–7.8)	—
FMS (1)[e]	1.6 (0.4–6.4)	2.7 (0.7–9.6)	Not computable due to zero cells	—
FMS (2)[e]	13.6 (3.0–60.6)	0.3 (0.0–1.5)	2.5 (0.4–17.2)	—

[a] Each odds ratio is the result of an equation in a logistic regression analysis with one EPS as dependent variable and one other EPS as independent variable adjusted for all other variables measured; e.g., in patients with tardive dyskinesia the probability of having akathisia is increased 6.6 times compared to patients without tardive dyskinesia.
[b] As defined by case definition (see Methods).
[c] AIMS converted to a trichotomous variable: AIMS score of 0 is the reference category; AIMS (1) is AIMS score of 1–9; AIMS (2) is AIMS score of 10 to highest score.
[d]UPDRS converted to a trichotomous variable: UPDRS score of 0 is the reference category; UPDRS (1) is UPDRS score of 1–11; UPDRS (2) is UPDRS score of 12 to highest score.
[e] Fahn–Marsden rating scale score converted to a trichotomous variable: Fahn–Marsden scale score of 0 is the reference category; FMS (1) is Fahn–Marsden score of 1–9; FMS (2) is Fahn–Marsden score of 10 to highest score.

Table 3
Prevalence of combinations of extrapyramidal syndromes ($N=194$) (percentages in descending order)

Combination of EPS	*N*	%
Tardive dyskinesia and parkinsonism	25	12.9
Tardive dyskinesia and tardive dystonia	19	9.8
Tardive dyskinesia and akathisia	10	5.2
Parkinsonism and tardive dystonia	9	4.6
Parkinsonism and akathisia	5	2.6
Akathisia and tardive dystonia	2	1.0

and below 500 mg CPZEQ, which is often considered as a border between low and moderate to high dose). In the patients with less than 500 mg CPZEQ, having tardive dyskinesia reduced the probability of having akathisia (OR of 0.3), whereas the opposite was the case in patients using more than 500 mg CPZEQ; in the latter, tardive dyskinesia increased the probability of having akathisia (OR 8.8).

In patients with tardive dyskinesia, the probability of having tardive dystonia as well is strikingly increased. One clinical consequence of this finding is that diagnosing tardive dyskinesia must alert the clinician to look for tardive dystonia, a disorder that is often overlooked. Since tardive dystonia causes more distress to the patient than tardive dyskinesia (Burke, 1992), switching to an atypical neuroleptic like clozapine may be a successful strategy (van Harten et al., 1996b).

Another finding in this study was that parkinsonism was inversely related to both tardive dyskinesia and tardive dystonia. The inverse relationship between tardive dyskinesia and parkinsonism has also been reported by others (Chouinard et al., 1979; Toenniessen et al., 1985; Kucharski et al., 1987; Gerlach, 1988; Gerlach et al., 1993). Previously, it was hypothesized that tardive dyskinesia and parkinsonism represented opposite pathophysiological states, with an excess of dopamine in the former and a deficiency of dopamine in the latter. However, quite often both syndromes co-exist, which makes such a hypothesis less likely. A possible alternative hypothesis is that parkinsonism is a forerunner of tardive dyskinesia, as has

been proposed by several authors (Gardos and Cole, 1992; Kane et al., 1986). As far as we know, we are the first to report that having parkinsonism reduces the probability of having tardive dystonia. A possible explanation is that tardive dystonia and tardive dyskinesia share a common etiology. In the past many researchers have considered dystonic features a variant of tardive dyskinesia (Task Force on Tardive Dyskinesia, 1992). Burke (1992), on the other hand, argued that tardive dystonia should be regarded as distinct from classic tardive dyskinesia because (1) it has different phenomenologic manifestations, (2) patients with tardive dystonia are younger at onset, and lack the female predominance seen with tardive dyskinesia, and (3) the pharmacological reactions involved are different (tardive dystonia is sometimes alleviated by anticholinergics and tardive dyskinesia is sometimes exacerbated by anticholinergics).

This study shows that EPS is a common phenomenon in this population: only one quarter of the patients had no signs of EPS, whereas almost 30% had two or more EPS. Furthermore, in the subgroups of our patients with at least one EPS, most had two or more EPS. As mentioned above, we are aware of only two studies that have been conducted in a geographically well-defined catchment area (McCreadie et al., 1992; O'Hara et al., 1993). The Nithsdale schizophrenia study assessed tardive dyskinesia, parkinsonism and akathisia simultaneously; results showed that 44% of the patients in that study had no EPS, whereas 20% had two or more EPS (McCreadie et al., 1992). The lower prevalence of EPS in the Nithsdale schizophrenia study may have been due to the lower mean age of that population. The study by O'Hara et al. (1993) assessed tardive dyskinesia and parkinsonism simultaneously in long-term psychiatric patients in day-care in south London and reported prevalences of 15% and 21%, respectively. These percentages are much lower than ours and also lower than those reported by others (Task Force on Tardive Dyskinesia, 1992). The authors did not provide any explanation for the difference (O'Hara et al., 1993). In many other studies the prevalence of the combination of tardive dyskinesia with parkinsonism in the population studied ranges from 5.5 to 24% (Gardos and Cole, 1992; Richardson and Craig, 1982; Hansen et al., 1992). However, an obvious problem in comparing the studies is the heterogeneity of the populations and the measurements employed.

Although there is an inverse relationship between tardive dyskinesia and parkinsonism, the prevalence of the coexistence was as high as 12.9%. This combination constitutes another clinical dilemma, since administering anticholinergics relieves parkinsonism, but may increase the severity of tardive dyskinesia (Jeste and Wyatt, 1982). Currently, there is no method of treating both simultaneously. However, in clinical practice it is advisable to treat the condition about which the patient complains most; very often this is parkinsonism (Yassa and Nair, 1988).

We would like to stress that the inter-relationships between the EPS were revealed in this study by the use of multivariate techniques; most relationships disappeared when only the crude OR was computed. This may partly explain why other studies that used only univariate techniques did not find these associations (Sethi et al., 1990; Halstead et al., 1994), and shows the importance of taking into account the effect of possible confounders.

The cross-sectional design of our study does not permit us to distinguish between factors that affect EPS development and factors that affect the course of the EPS once it has occurred. Therefore, this study cannot address relationships between different EPS over time. Furthermore, cross-sectional studies are particular vulnerable to selection biases. The inclusion of nearly all psychiatric inpatients in a circumscribed area reduces the selection bias. This, in combination with the fact that the medical history of these patients is documented in a single file by Western doctors, should mean that the data can be extrapolated to other psychiatric inpatients. However, it could be possible that in our area, with a mainly Afro-Caribbean population, the cultural setting did influence the characteristics of the population. Indeed, the population has some unusual characteristics: a male–female ratio of 2.7, a low prevalence of affective disorders, and a 12% prevalence of leukotomy. These variables were controlled for in the analysis.

One might wonder whether the raters were able

to make a clear distinction between the various EPS, in particular between the hyperkinetic syndromes (tardive dyskinesia, akathisia, tardive dystonia). As was mentioned, however, the raters were well trained and most of the time they were able to differentiate between the pattern of normal, restless movements of akathisia, the abnormal movements of dyskinesia and the twisted movements of dystonia. Moreover, akathisia was defined as both subjective complaints of restlessness and objective motor movements, typically movements of the legs (Barnes, 1989). However, no differentiation could be made between akathisia and tardive akathisia.

In conclusion, our study has shown that there are strongly positive correlations between hyperkinetic forms of EPS. More specifically, the probability of having akathisia, which is often neglected or misdiagnosed, is markedly increased in a patient suffering from tardive dyskinesia. Furthermore, it is quite common for chronic psychiatric inpatients to suffer from combinations of EPS. Therefore, it is definitely advisable that psychiatrists dealing with such patient groups should be familiar with treatment strategies for minimizing these EPS and should regularly check on the state of the EPS.

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